

1996 ABSTRACT FORM - AMERICAN SOCIETY OF HUMAN GENETICS

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Chromosomes X, Y, and 21 aneuploidies in sperm of men who ingested ultra-high doses of diazepam. A. Baumgartner^{1,2}, A.E. Czeizel³, I.-D. Adler², X. Lowe¹, T.E. Schmid², and A.J. Wyrobek¹. ¹Bio. Biotech. Res. Prog., Lawrence Livermore Natl. Lab., Livermore, CA; ²GSF-Institut für Säugetiergenetik, Neuherberg, Germany; ³Department of Hum. Genetics and Teratology, Natl. Inst. of Hygiene, Budapest, Hungary.

Drugs which induce aneuploidy in human germ cells may also lead to increased incidences of spontaneous abortions and various aneuploidy syndromes among liveborn offspring. Diazepam (Valium®) is widely administered as a sedative, muscle relaxant and anxiolytic drug. We selected it for testing as a potential human germinal aneugen because it has inhibited centriolar separation in cultured human fibroblasts and produced aberrant spindles in rodent germ cells. Five young non-smoking men who were hospitalized after their suicide attempt using diazepam, ~1-7 mg/kg (oral intake), provided semen samples 40-50 days and ~100 days after exposure to assess drug effects on meiotic cells and to evaluate persistence, respectively. Five healthy men served as local clinical controls. A multicolor FISH assay was applied to detect aneuploidy for chromosomes X, Y, and 21 in sperm. Sex ratios were not significantly different from 1:1 among 133,143 cells analyzed. The 40-day samples of the diazepam-exposed patients showed an increase in several sperm aneuploidy groups: disomy 21 (1.5 fold, $p=0.04$); disomy X (2.7 fold, $p=0.0006$) and XY aneuploidy (1.6 fold, $p=0.017$). The results for ~100 days after exposure were similar to those of the controls suggesting that the aneuploid effects may not persist. Our findings are consistent with the possible aneuploidy-inducing effect of diazepam during male meiosis but further studies are needed before these results can be extrapolated to therapeutic dosing because suicide patients are a highly exposed cohort and other confounding factors (alcohol, drugs, antidotes) cannot be ruled out. [Work was performed under the auspices of the US DOE by the Lawrence Livermore Natl. Lab. under contract W-7405-ENG-48; A.B. was supported by EU contract EV5V-CT94-0403 and the US DOE]

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